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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/607,996	06/30/2003	Shigehiko Imagawa	239620US0	8187

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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/607,996	IMAGAWA ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *Oct 6, 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

This application claims benefit to a provisional application No. 60/391952, filed on 6/28/2002, in a language other than English. Applications that claim benefit of a provisional application filed in a non-English language must include an English translation of the non-English language provisional application and a statement that the translation is accurate unless the translation and the statement were previously filed in the provisional application. See 37 CFR 1.78(a)(5). The translation as required by 37 CFR 1.78(a)(5) has not been filed in this application. Applicant must supply the missing translation in the reply to this Office action prior to the expiration of the time period set in this Office action. See MPEP § 201.15.

In the absence of an English translation of provisional application No. 60/391952, the filing date of the instant claims is deemed to be the filing date the instant application, June 30, 2003. If Applicant disagrees, Applicant should present a detailed analysis as to why the claimed subject matter has clear support in earlier priority applications. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 USC § 112, first paragraph.

Claims 1-20 are pending in this application and examined on the merits herein.

Claim objections

Claim 5 objected to because of the following informalities: The claim recites the phrase, "ishypoplastic anemia," which does not denote any known

pathological condition. The correct phrase is likely, "is hypoplastic anemia."

Appropriate correction is required.

35 USC § 102 Rejections

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15 and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by Imagawa et. al. (Reference included in PTO-892) Imagawa et. al. discloses, "the ability of **K-7174** [a GATA-specific inhibitor, also known as N,N'-bis(5-(3,4,5-trimethoxyphenyl)-4-pentenyl)homopiperazine, the same compound used in the claimed therapeutic methods in the instant claimed invention] to **improve Epo [erythropoietin] production** when Epo production was inhibited by IL-1β, TNF-α, or L-NMMA." (end of first paragraph). The procedure disclosed in this reference involves administering K-7174 to a culture of Hep3B cells. This procedure involves the same compound, procedure, and cell line used in the experimental protocol described under the heading examples on pp. 7-8 of the instant specification. The result of this procedure is an increase in erythropoietin production similar to that described in the instant application. Imagawa et. al. clearly teaches "A method for potentiating erythropoietin production

comprising contacting a cell which can produce erythropoietin with an effective amount of [the compound K-7174 or a hydrate or addition salt]." Therefore the claimed invention is anticipated by the disclosure of Imagawa et. al. which anticipates the use of K-7174 to increase erythropoietin production *in vivo* in claims 15 and 17, as it achieves the same result by the same method as the claimed invention.

Claims 15, 16, and 18-20 are rejected under 35 USC 102(b) as being anticipated by Nakao et. al. (US patent 5723456, cited in PTO-892).

Nakao et. al. discloses that N,N'-bis(5-(3,4,5-trimethoxyphenyl)-4-pentenyl)homopiperazine (referred to as compound 1 or 2, see col. 6, lines 31-39) is useful as a cell adhesion inhibitor and as a therapeutic for the treatment of inflammations, asthma, rheumatism, and arteriosclerosis in animals, including humans (See claim 2, col. 10, lines 34-62). In the process, they disclose several animal models used to demonstrate their results, including Guinea pig asthma (table 2, col. 7, lines 50-60), mouse contact dermatitis (table 3, col. 8, lines 16-27), and rat carrageenin-induced inflammation (table 4, col. 8, lines 48-59). In these tables, N,N'-bis(5-(3,4,5-trimethoxyphenyl)-4-pentenyl)homopiperazine is referred to as compound 1 for the Z isomer and compound 2 for the E isomer. The amount administered was approximately 10 mg/kg in each test.

Page 7, lines 5-6 of the instant specification discloses a range of possible doses to be administered in the methods of the claimed invention, ranging from 0.01 to 1000

mg per day. Nakao et. al. discloses an effective dose between 0.1 and 1000 mg per day (Col. 3, lines 56-62) in a single dose, or divided into two or three doses. In particular, examples 6 and 7 (col. 9, lines 25-53) disclose a formulation in the form of capsules or tablets, each comprising 30 mg of the active ingredient N,N'-bis(5-(3,4,5-trimethoxyphenyl)-4-pentenyl)homopiperazine. Thus the dose disclosed by Nakao et. al. falls entirely within the dosage range taught by the instant specification.

Moreover, the instant claims 15, 16, and 18-20 merely recite, "a cell" or "a subject". Hence these claims are not limited to any particular cell or subject.

Therefore, as all three of the species possess erythropoietin-producing cells, the experimental protocols disclosed in this reference inherently involve, "contacting a cell which can produce erythropoietin with an effective amount of [K-7174]," in the language of claim 15, and would have had the effect of, "increasing the numbers of red blood cells or megakaryocytes in a subject," in the language of claim 20. The steps disclosed are the same as in the instant claims, administering the same compound in the same amounts to the same or similar cells or subjects. See *Ex parte Novitski* 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993). Note that the claiming of a new use, new function, or unknown property which is inherently present in the prior art does not make the claim patentable. See *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also *Eli Lilly and Co. v. Barr Laboratories Inc.* 251 F3c. 955; 58 USPQ2d 1869-1881 (Fed. Cir. 2001) with regard to inherency as it relates to the claimed invention herein.

Thus Nakao et. al. anticipates claims 15, 16, and 18-20

35 USC § 103 Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being obvious over Umetani et. al. (Reference included with PTO-892) in view of La Ferla et. al. (Reference included with PTO-892) and Applicant's admission regarding the prior art in the section, "background of the invention". (p. 1, lines 22-27)

Umetani et. al. teach that the compound N,N'-bis(5-(3,4,5-trimethoxyphenyl)-4-pentenyl)homopiperazine (herein referred to as K-7174) inhibits cell adhesion and VCAM-1 expression by binding to GATA DNA motifs and influencing gene expression. (p. 372, right column, p. 373, right column, third paragraph. This reference does not explicitly teach that K-7174 is useful for treating diseases caused by reduced erythropoietin production, potentiating erythropoietin production, or increasing the number of red blood cells or megakarocytes in a cell or subject.

La Ferla et. al. teach that the GATA binding protein GATA-2 is involved in the regulation of erythropoietin production during hypoxia. In particular, they state, "HepG2 cells showed strong GATA-2 DNA binding in normoxia (Fig. 5A), which was reduced upon exposure of the cells to hypoxia. Stimulation with IL-1β or TNF-α for 4h led to an

increase in GATA-2 DNA binding in hypoxia." (Results, Induction of GATA-2 DNA binding by IL-1β and TNF-α) They further demonstrate that, "with respect to Epo production, Il-1β induced only a moderate decrease when GATA-2 function was blocked by treating cells with a GATA binding oligonucleotide." (Results, Influence of IL-1β and TNF-α on Epo promoter activity, second paragraph.) These results demonstrate that the GATA binding motif and its associated transcription factors play an important role in the induction of erythropoietin production during hypoxia, and in its suppression by chronic inflammatory diseases (the anemia of chronic disease, or ACD), and that disrupting the binding of transcription factors to this motif leads to an increase in erythropoietin production by the treated cell.

It is known that a number of pathological conditions result from reduced production of erythropoietin, and that increasing erythropoietin levels, usually by injection of recombinant erythropoietin, is a useful therapeutic method for said conditions. For example, page 1 of the instant specification states that, "Clinically, Epo is used in treatment of anemia associated with chronic renal failure (CRF), autologous blood shortage, or anemia of prematurity. (p. 1, lines 22-24)

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Umetani et. al. and La Ferla et. al. by using K-7174 to stimulate erythropoietin production in a cell, whether *in vitro* or *in vivo*, by disrupting the binding of GATA-2 to the GATA motif, thus simulating the transcriptional effects of hypoxia. It would also have been obvious to use said compound to rescue erythropoietin production that has been inhibited by TNF-α and IL-1. It would have also

been obvious to use such a treatment to improve the hemocrit and red blood cell count in patients suffering from erythropoietin-responsive anemia, particularly anemia of chronic disease (ACD), and also to use K-7174 *in vitro* to increase erythropoietin production in a cell culture of HepG2 or other erythropoietin-producing cells.

One of ordinary skill in the art would have been motivated to modify the invention in this manner in order to treat patients suffering from pathological conditions caused by reduced production of erythropoietin. A treatment which would increase erythropoietin production within a patient's own cells would be useful for treating diseases currently treated by administration of recombinant erythropoietin." One of ordinary skill in the art would also be motivated to apply this method *in vitro* in the manner of claim 17 in order to increase artificial production of recombinant erythropoietin. Furthermore, one of ordinary skill in the art would have also known that this small molecule therapeutic would have been an improvement over recombinant erythropoietin because, "demand exists for a method for potentiating erythropoietin production through administration of a compound other than erythropoietin, as EPO exhibits poor bioavailability." (Instant specification, p. 2, lines 16-18)

One of ordinary skill in the art would have reasonably expected success because K-7174 was already known to be a useful pharmaceutical compound for the treatment of a number of pathological conditions, indicating that it possesses favorable pharmacokinetic properties.

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 1-3 and 7 are rejected under 35 U.S.C. 103(a) as being obvious over Nakao et. al. (U.S. Patent No. 5723456, which shares the same assignee as the instant application) in view of the Merck Manual, seventeenth edition (PTO-892 included). Nakao et. al. claims, in its second claim (col. 10, lines 34-62), "A preventive or therapeutic method for Pathological conditions selected from the group consisting of allergic diseases, asthma, inflammations, rheumatism, and arteriosclerosis, which comprises administering to a subject in need thereof an effective amount of a compound of the following formula (1)," in which formula 1 (found in col. 1, lines 15-30) includes several chemical structures, one of which is that of K-7174. Nakao et. al. does not explicitly teach the use of said compound for the treatment of anemia.

The Merck Manual teaches that Anemia of Chronic Disease (ACD), a form of anemia that accompanies an underlying inflammatory disease, involves several mechanisms one of which is that, in response to the underlying disease, "EPO production and marrow responsiveness are decreased, resulting in deficient erythropoiesis." (P. 861, left column, third paragraph) In other words, ACD is a "pathological condition caused by reduced production of erythropoietin," in the language of claim 1 of the instant specification. Regarding treatment, this reference teaches, "Treating the underlying disease is most important. Because the anemia is generally mild, transfusions are usually not required and recombinant EPO frequently corrects the anemia with fewer or no transfusions." (P. 861, right column, third paragraph) Therefore one of ordinary skill in the art at the time of the invention would have been motivated to

modify the teaching of Nakao et. al. by administering the anti-inflammatory therapeutics claimed therein to a subject suffering from ACD.

One of ordinary skill in the art would be motivated to modify the teaching of Nakao et. al. in this manner in order to improve the erythropoietin production of the subject's erythropoietin-producing cells, subsequently increasing their red blood cell count and reversing the patient's anemia, by reducing the inflammatory condition that was ultimately responsible for the reduced erythropoietin production in the first place. One of ordinary skill in the art would have reasonably expected success because K-7174 was already established as being effective for the treatment of inflammatory diseases, and treatment of the underlying inflammatory disease was the state of the art for the treatment of ACD caused by an underlying inflammatory disease.

This procedure is included within the scope of claims 1-3 and 7 because it is clearly described by the language, "A method of treating a pathological condition caused by reduced production of erythropoietin, comprising: administering to a subject in need thereof an effective amount of one of the following compounds: [K-7174 or its acid addition salts and hydrates]."

Therefore the invention taken as a whole is *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 and 7-16, and 18-20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 2 of Nakao et. al. (U.S. Patent No. 5723456, which shares the same assignee as the instant application) in view of the Merck Manual, seventeenth edition (PTO-892 included). Nakao et. al. claims, in its second claim, "A preventive or therapeutic method for Pathological conditions selected from the group consisting of allergic diseases, asthma, inflammations, rheumatism, and arteriosclerosis, which comprises administering to a subject in need thereof an effective amount of a compound of the following formula (1)," in which formula 1 (found in col. 1, lines 15-30) includes several chemical structures, one of which is that of K-7174. Nakao et. al. does not explicitly teach the use of said compound for the treatment of anemia.

The Merck Manual teaches that Anemia of Chronic Disease (ACD), a form of anemia that accompanies an underlying inflammatory disease, involves several mechanisms one of which is that, in response to the underlying disease, "EPO

production and marrow responsiveness are decreased, resulting in deficient erythropoiesis." (P. 861, left column, third paragraph) In other words, ACD is a "pathological condition caused by reduced production of erythropoietin," in the language of claim 1 of the instant specification. Regarding treatment, this reference teaches, "Treating the underlying disease is most important. Because the anemia is generally mild, transfusions are usually not required and recombinant EPO frequently corrects the anemia with fewer or no transfusions." (P. 861, right column, third paragraph) Therefore one of ordinary skill in the art at the time of the invention would have been motivated to modify the teaching of Nakao et. al. by administering the anti-inflammatory therapeutics claimed therein to a subject suffering from ACD.

One of ordinary skill in the art would be motivated to modify the teaching of Nakao et. al. in this manner in order to improve the erythropoietin production of the subject's erythropoietin-producing cells, subsequently increasing their red blood cell count and reversing the patient's anemia, by reducing the inflammatory condition that was ultimately responsible for the reduced erythropoietin production in the first place. One of ordinary skill in the art would have reasonably expected success because K-7174 was already established as being effective for the treatment of inflammatory diseases, and treatment of the underlying inflammatory disease was the state of the art for the treatment of ACD caused by an underlying inflammatory disease.

This procedure is included within the scope of claims 1-3 and 7-14 because it is clearly described by the language, "A method of treating a pathological condition caused by reduced production of erythropoietin, comprising: administering to a subject

in need thereof an effective amount of one of the following compounds: [K-7174 or its acid addition salts and hydrates]." Since such a treatment will have the effect of increasing the number of red blood cells in the patient, it also falls within the limitations of claim 20. It is also included in the scope of claims 15, 16, 18, and 19 because it involves in the language of claim 15, "A method for potentiating erythropoietin production comprising contacting a cell which can produce erythropoietin with an effective amount of one or more of the following compounds: [K-7174 or its acid addition salts and hydrates]." In this case, the cell in question is *in vivo*, inside a subject suffering from ACD, and the method of contacting the cell is by systemically administering the compound to the subject.

Summary

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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